REMARKS

CLAIM REJECTIONS UNDER 35 USC §102

NOVELTY REJECTIONS BASED ON DURRANT ET AL., 1993

The Examiner states "Durrant et al. disclose a rat polyclonal antiserum that comprises purified immunoglobulin anti-idiotypic antibodies that evidence the Lewis B antigen epitope confirmation, which would specifically bind to and form a complex with *Helicobacter pylori* Lewis B antigen binding antigen as Durrant showed that the rat antiserum comprised anti-ID Lewis B antigen presenting immunoglobulins."

The Examiner points to Essery et al to show that an anti-idiotypic antibody which evidences the Lewis B antigen structure disclosed in Durrant would bind to the BabA protein which binds to Lewis B antigen. Essery discloses that 1 of 3 strains of *Helicobacter pylori* bound to the anti-id Lewis A IgG monospecific antibody. Applicants respectfully traverse.

As discussed by Dr. Hammarström in the accompanying Declaration, the antibodies against Lewis A and Lewis B recognize unique antigens and the specificity is due to sequence differences in the hypervariable region. Dr. Hammarström states that thus, by definition, the anti-idiotypic antisera raised by Essery et al. are not directed against the antigen binding site, but rather a paratope which is shared to some, albeit modest, degree that binds the tested monoclonals (anti- Lewis A and anti- Lewis B). Dr. Hammarström points out that the reference claims that this paratope is not shared with 4 other monoclonal antibodies, but no

data is provided to support this claim (see Essery et al., page 19 "Specificity of the proteins A sepharose reagent"). In fact, Essery et al. states, "the paratope of the Fab portion of the anti-idiotypic antibody appears to have a structure similar to the Lewis A antigen" (emphasis added), it does not say identical to the Lewis A antigen.

Dr. Hammarström indicates that if one believes that there is indeed specific binding to the anti-idiotypic antiserum to BabA, it follows that this antigen is also present on other bacteria, such as *N. gonorrhoeae,* and fungi such as *C. ablicans.* Here, 1 of 2 *N. gonorrhoeae* strains reacted (see page 19, column 2, last paragraph, lines 5-7) and 1 of 2 *C. ablicans* strains reacted (see page 20, column 1, first paragraph, lines 5-8). But since these microorganisms do not express BabA, Dr. Hammarström states that the anti-idiotypic antiserum described by Essery et al. **must** recognize **another** protein or structure.

Applicants also note that the claims have been amended to require that the BabA protein binds both Lewis B and H-1 blood group antigen-glycoconjugates. This is missing from Durrant.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

NOVELTY REJECTIONS BASED ON UEMURA ET AL (U.S. 5,258,177)

The Examiner has rejected claims 3-8, 16, 19 and 27-30 as being anticipated by Uemura et al. in light of evidence provided by Boren et al. The Examiner contends that the monospecific immunoglobulin compositions of Uemura et al. that comprise

secretory sIgA from human colostrum specifically bind BabA because the claims do not specifically recite that the claimed antibodies bind to BabA via the antibody hypervariable region. Applicants respectfully traverse.

As Dr. Hammarström states, stating the fact that the specific binding is carried out by the antigen binding site of the specific antibody, as determined by the sequence of the hypervariable region is superfluous because those of skill in the art understand that this is the case. He further states that if binding to a sugar moiety on some antibodies would confer specific binding, there would be no need for immunization in order to raise anti-BabA-specific antibodies.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

CLAIM REJECTIONS UNDER 35 USC §103

The Examiner has rejected claim 2 as obvious over Boren (1995) in view of Foster et al. (U.S. Pat. No. 4,444,879). The Examiner contends that Boren teaches detection of the presence of a *Helicobacter pylori* blood group binding protein antigen using binding of colostum sIgA in a method of detecting the presence of absence of the blood group antigen in a sample. The Examiner acknowledges that Boren fails to show the incorporation of the IgA immunoglobulin/antibody into kit form.

The Examiner contends that Foster et al. discloses formulation of immunoglobulin/antibody compositions into kit form. Based on these disclosures, the Examiner contends that it would have been

obvious for a person skilled in the art to modify the Boren composition and form a kit as taught by Foster to obtain the present invention. The Examiner's reasons for why the skilled artisan would be motivated to do so are lengthy (see page 13 of the Office Action) and are not repeated here. Applicants respectfully traverse.

It would appear that the Examiner is using impermissible hindsight in order to frame the rejection, which is improper. The Boren et al. publication reports experiments identifying the receptor on the surface of gastric mucosal cells to which *H. pylori* proteins bind in the process of attaching to gastric mucosal cells. Specifically, Boren et al. reports that pre-incubation of *H. pylori* with secretory IgA isolated from human colostrum inhibited subsequent binding by *H. pylori* to gastric mucosal cells. In contrast, the same pre-incubation experiment conducted with IgA antibodies isolated from serum failed to inhibit *H. pylori* binding to gastric mucosal cells (see pg 32). The conclusion drawn from this experiment is that the colostrum secretory IgA antibodies present the same attachment-mediating receptor to *H. pylori* that the gastric mucosal cells do.

The distinction between secretory IgA antibodies isolated from colostrum and IgA antibodies isolated from serum is that the colostrum secretory IgA antibodies are conjugated with carbohydrate whereas serum IgAs are not. Based on this distinction, Boren et al. ran experiments with monoclonal antibodies directed against carbohydrate antigens, specifically the Lewis A and Lewis B antigens. Only secretory IgA isolated from colostrum detected Lewis A and Lewis B antigens: the Lewis antigens were not detected

by IgA antibodies from sera. The conclusion that Boren et al. draws from this result is that Lewis A and Lewis B carbohydrates are candidates for the receptor to which *H. pylori* binds to attach to gastric mucosal cells (see Boren et al. (1993) Science 262:1892-1895; attached).

Through additional experiments, Boren et al. identifies Lewis B protein conjugates as potent inhibitors of *H. pylori* attachment to gastric mucosal cells, whereas Lewis A protein conjugates do not have such inhibitory activity. The conclusion drawn here is that "Lewis B antigen is an essential part of the cell surface H. pylori receptor" (see Boren and Falk, 1995, page 32). At no point does Boren et al. describe any antisera or antibody that binds to the adhesion protein via its hypervariable region. That is, the secretory IgA molecules do not specifically bind adhesin, rather adhesion specifically binds the fucosylated Lewis B antigen presented on the secretory IgA molecule.

As Dr. Hammarström points out, normal antibodies demonstrate binding properties due to the variable domains of the antibody, whereas the Boren paper describes the ability of the *H. pylori* **adhesion protein** (BabA) to bind to Lewis b antigens present on glycosylated proteins (an IgA antibody preparation) in human milk. He notes that the paper also describes a similar IgA antibody preparation purified from human sera, which are the IgA antibodies that are present in human blood. These human blood antibodies are low in glycosylation and do not present Lewis b antigens. As a consequence, and as Dr. Hammarström points out, they do not inhibit bacterial binding because the H. pylori Lewis b binding adhesion protein (BabA) does not bind to non-glycosylated antibodies.

The instant application describes **monospecific** antisera and antibodies raised against BabA protein from *Helicobacter pylori* that specifically recognize and bind to BabA protein through their hypervariable region. Stated clearly, the Boren et al. antibodies bind to a carbohydrate antigen, the Lewis B carbohydrate, whereas the antisera and antibodies of the present invention bind to protein antigen, the adhesin protein of *H. pylori*. Thus, there would not be any motivation for the skilled artisan to modify the Boren composition.

The Foster et al. reference does not fill the void present in the Boren et al. reference simply because Foster teaches kits containing immunoglobulin/antibody compositions.

In view of the above, Applicants respectfully request reconsideration and removal of the rejections.

Applicants submit that the claims remaining in the case, define non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is requested to contact Susan W. Gorman (Reg. No. 47,640) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,
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0825-0176P

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Attachments: Declaration of Dr. Lennart Hammarström